Towards a New Regulatory Framework for Human Cells and Tissues

FDA and the New Paradigm for Tissue Regulation

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Towards a New Regulatory Framework for Human Cells and Tissues

- Why is Oversight Needed?
- How to Regulate?
  - FDA's Proposed Approach
  - Overview of FDA Rules
- Advantages and Challenges of FDA Approach
- Priorities in Going Forward

Why Is Oversight Needed?
Rapidly Growing Industry

- Number of musculoskeletal tissue transplants in U.S. alone increased from approximately 350,000 in 1990 to 1,000,000 in 2004
- New techniques for processing and manipulating human cells and tissues
- Growth in development of “tissue engineered” products consisting of tissue + device
- Promise of hematopoietic stem cells for hematopoietic reconstitution
- Increasing international commerce in tissues

Why Is Oversight Needed?
Public Health Concerns Increasing

- 1980's --'90's: CJD transmitted by dura mater, eye tissue
- 1992: Seven people infected with HIV through transplantation of organs and tissue (single donor)
- Since 1997, over 50 reports in the U.S. of bacterial/fungal infections from tissues
- 2002: West Nile Virus transmitted by blood and organ donation; potential risk for tissues
- 2002: Organ and tissue recipients infected with hepatitis (single donor)
- Emerging disease agents pose potential threats

Why Is Oversight Needed?
Additional Considerations

- Public expectation for safety is high
- Over 100 transplants from a single donor – many at risk if inadequate communicable disease risk assessment
- Tests not always available and not foolproof
- Industry standards not always followed and are unenforceable
- Demand for tissue/cell products likely to increase
- Perception of poorly regulated industry could thwart tremendous technological promise

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Why Develop a New Regulatory Approach?

- U.S. approach was fragmented
  - Tissues/cells did not always fit regulatory “pigeon holes”
  - Some products highly regulated; e.g., cell-based gene therapies
  - Some tissues/cells not actively regulated; e.g., hematopoietic stem cells derived from cord blood, peripheral blood
  - Some tissues minimally regulated; concerns about safety

Why Develop a New Regulatory Approach?

- We had the opportunity to develop a risk-based framework
  - Legislative proposals for hematopoietic stem cells pending
  - Highest levels of FDA management engaged
  - Positive feedback from industry, academia, consumer groups

How to Regulate?
Practical Limitations

- Relied on existing law
  - Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq.
  - Public Health Service Act, 42 U.S.C. 262, 264
- Organs, bone marrow excluded (in the U.S., these are the purview of HRSA)
- Blood and blood products excluded because regulation longstanding and highly developed
- Challenge of regulating previously unregulated products; e.g., hematopoietic stem cells

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How to Regulate?
Practical Limitations

- Xenotransplantation excluded because different infectious agents of concern and broad interagency and international coordination sought
- Therapies often raise complex social and policy issues as well as scientific issues; e.g., cloning, embryonic stem cells, assisted reproductive technologies
- Limited resources

FDA's Proposed Approach
to the regulation of cell and tissue products

- Announced February 1997
- Risk-based approach to include a broad range of products
- The level and type of regulation should be commensurate with the risk posed by the product characteristic
- Like products should be treated alike
- FDA should exercise regulatory oversight only to the degree appropriate to protect the public health

FDA's Proposed Approach
Five Areas of Regulatory Concern

- Preventing transmission of communicable disease
- Safe processing and handling
- Clinical safety and effectiveness, where appropriate
- Promotional claims
- Monitoring of industry

FDA's Proposed Approach
Scope

- **Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)**
  - **musculoskeletal tissue**
  - **ocular tissue**
  - **cellular therapies**
  - **hematopoeitic stem cells**
  - **reproductive tissue**
  - **combination tissue/device; tissue/drug**
  - **human heart valve allografts**
  - **dura mater**

FDA's Proposed Approach
Not Included

- Vascularized organs
- Minimally manipulated bone marrow
- Xenografts
- Blood products
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products
- *In vitro* diagnostic products

Two Main Regulatory Tiers

- **Regulated solely under section 361 regulations if *ALL* "kick down" factors apply**
- **Regulated under section 361 regulations *AND* IND/BLA (or IDE/PMA) if HCT/P does not meet all "kick down" factors**

“Kick down” Factors

- Minimally manipulated
- Intended for homologous use only
- Not combined with another article
  - Exception: water, crystalloids, or a sterilizing, preserving, or storage agent
- Does not have systemic effect and is not dependent upon the metabolic activity of living cells
  - Exception: autologous use, use in first or second degree blood relative, reproductive use

Overview of FDA Rules
Registration and Listing

- Requires establishments to register with FDA and submit a list of their HCT/Ps
- Creates unified registration system
- Sets out criteria that FDA will apply in determining whether HCT/P is regulated solely under communicable disease requirements

Overview of FDA Rules
Donor Eligibility

- Testing and screening of most cell and tissue donors for relevant communicable diseases
  - Facilitates rapid adoption of testing/screening for newly identified agents
  - Type of testing/screening tailored to type of tissue
- Positive results = ineligible donor
- Exceptions: testing/screening not required for autologous donors, sexually intimate partner
- Flexibility for directed donors and emergencies

Overview of FDA Rules
Good Tissue Practice

- Methods, facilities, and controls for manufacturing to prevent infectious disease contamination
- Broad goals applicable to the wide range of HCT/Ps
- Establishments have the flexibility to determine how to meet goals through their own procedures
- Requires a quality program to prevent, detect, and correct deficiencies that could increase communicable disease risk

Good Tissue Practice

- Recover, process, store, label, package, and distribute HCT/Ps, and screen/test donors, to prevent introduction, transmission, and spread of communicable disease
- Communicable diseases include viruses, bacteria, fungi, parasites, and TSE agents
- Adverse reaction/deviation reporting and tracking requirements

Overview of FDA Rules
Additional Provisions

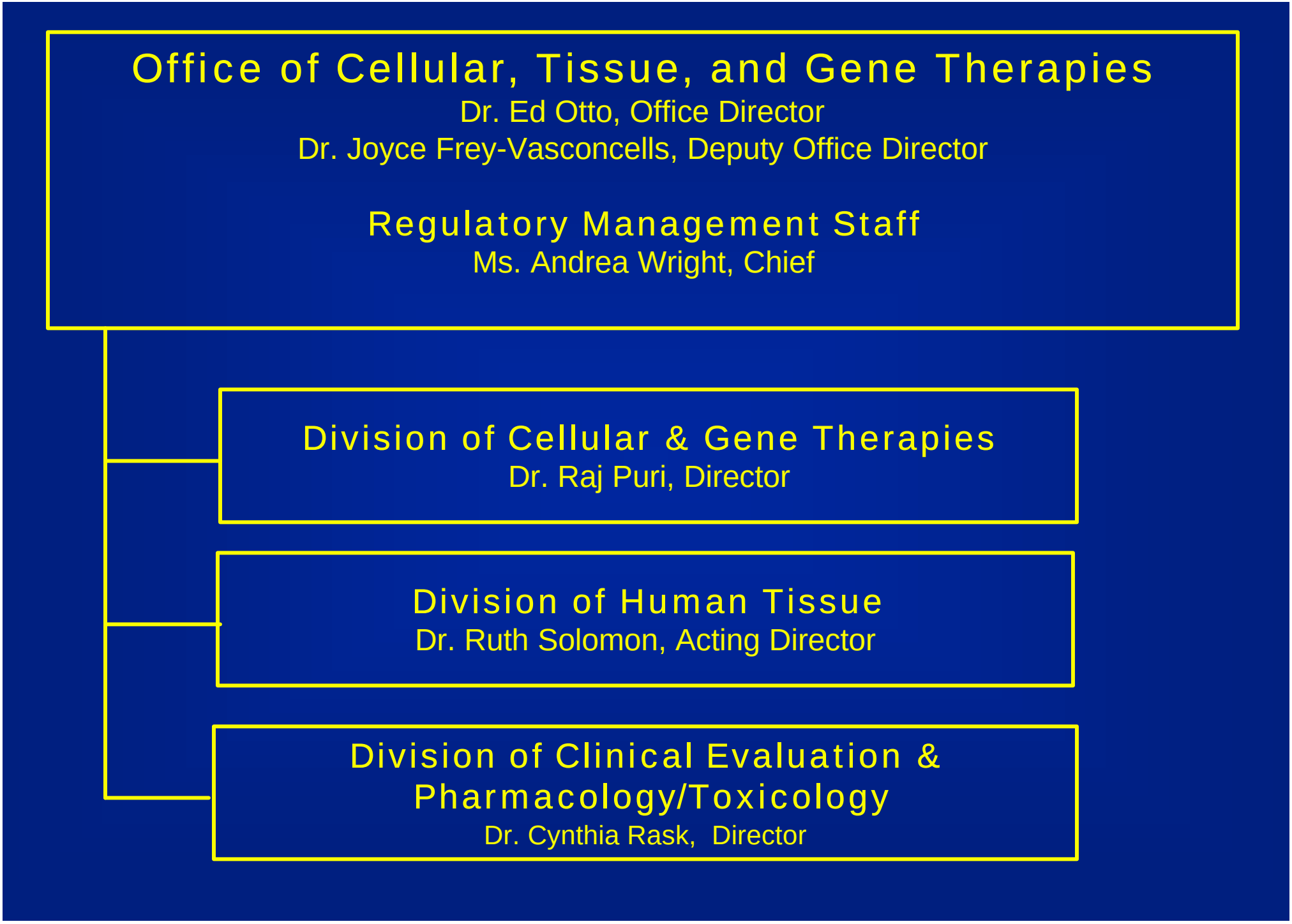
- Inspection authority
- Imports
- Enforcement authority
  - Orders of retention, recall, destruction, and cessation of manufacturing

Overview of FDA Rules
Regulatory Roll Out

- **Registration and Listing effective April 4, 2001, for currently regulated tissues**
- **Registration and Listing effective January 21, 2004 for all other firms/products covered by the regulations**
  - EXCEPT human heart valve allografts and dura mater (effective May 25, 2005)
- **Donor Eligibility final rule effective May 25, 2005**
- **Good Tissue Practice final rule effective May 25, 2005**

CBER Office of Cellular, Tissue, and Gene Therapies

- Began operations October 2002
- Responsible for regulatory/review activities for tissues, cellular and tissue-based products, gene therapies, xenotransplantation products
- Merged functions formerly contained in CBER, OBRR (Human Tissue Program) and OTRR (Division of Cellular and Gene Therapy)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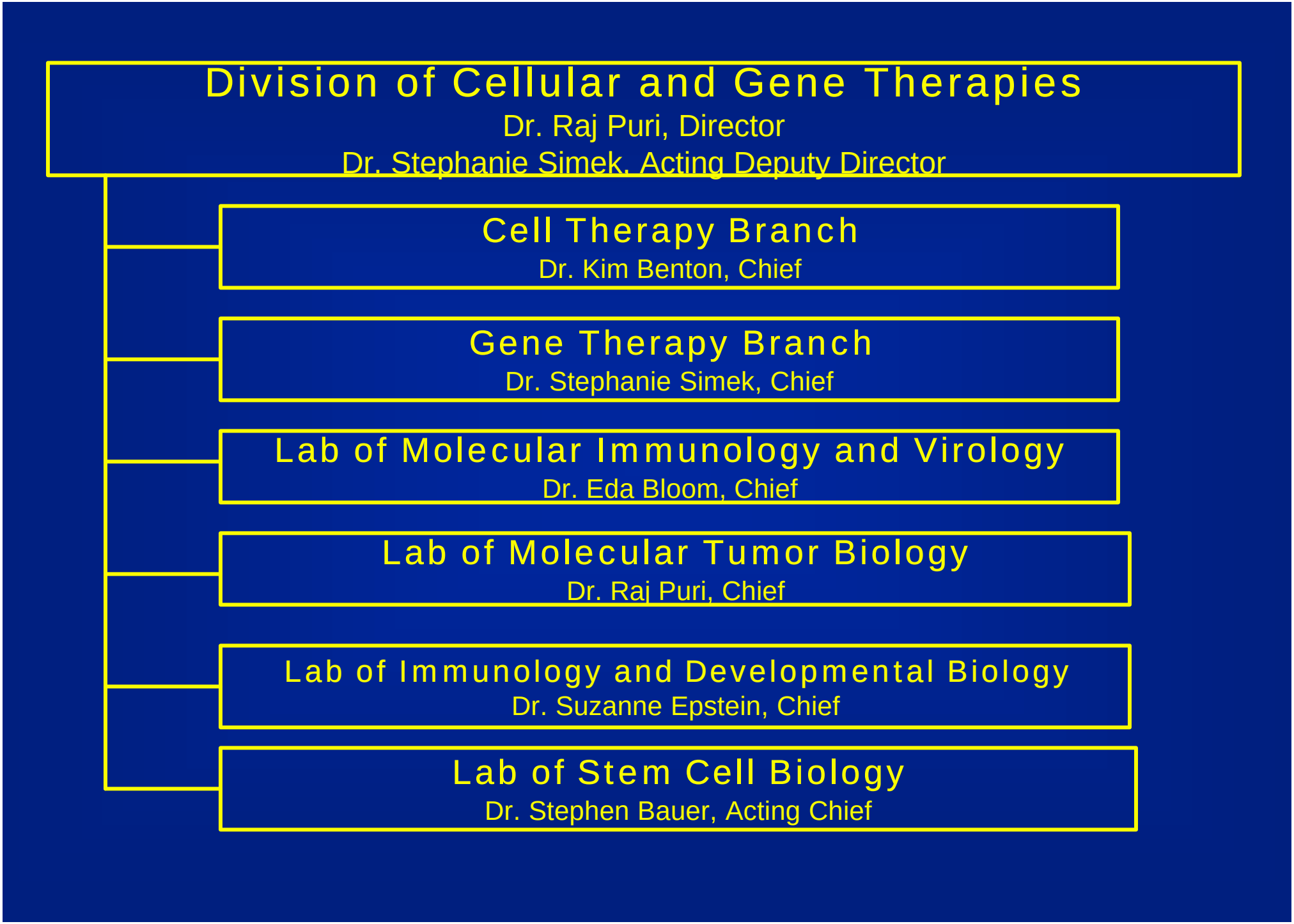
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Advantages of FDA Approach

- Unified, comprehensive regulatory framework
- Clear, enforceable requirements will protect the industry and help assure the continued availability of medically necessary products
- Predictable regulatory requirements support innovation
- Public confidence in HCT/Ps hinges on effective regulation
- Broad support from industry and the public
- Consistent with industry standards

Advantages of FDA Approach

- **Risk-based Approach**
  - **Tiered approach that provides appropriate type and level of regulation based on product characteristics**
  - **Platform of minimal requirements applies to all cells and tissues**
  - **Additional requirements added where necessary for safety, product effectiveness**
- **FDA approach used as model by other regulatory bodies**

Challenges of FDA Approach

- Reliance on existing statutory authority limits ability to address tissue quality and functionality
- Complexity and administrative procedures requirements have caused delay
- Challenge of transition from existing regulation to new framework
- Challenge to leverage limited resources for maximum impact on public health
- Ongoing issues such as efficient oversight of hospital-based treatments, ancillary products

Priorities in Going Forward

- Increase scope and depth of inspections
- Rapidly detect, analyze, and respond to adverse reactions relating to transmission of communicable disease
- Provide outreach, training, and guidance on implementation of new regulations
- Define licensure criteria for hematopoietic stem cells
- Collaborate with international stakeholders to enhance tissue/cell safety

For Further Information

- **Tissue: www.fda.gov/cber/tiss.htm**
- **Cellular and Gene Therapy: www.fda.gov/cber/gene.htm**